ELSEVIER
SAUNDERS

Urol Clin N Am 35 (2008) 91–99

UROLOGIC
CLINICS
of North America

# Re-imagining Interstitial Cystitis

Philip M. Hanno, MD, MPH

*Hospital of the University of Pennsylvania, 9 Penn Tower, 3400 Spruce Street, Philadelphia, PA 19104, USA*

**New developments in infection/inflammation in urology Re-imagining interstitial cystitis**

Since Keay [1] postulated an "antiproliferative factor" (APF) in 1998 and described this putative central protein in the etiologic pathway of the painful bladder syndrome/interstitial cystitis (PBS/IC) six years later [2], there have been no dramatic breakthroughs in the field. Although much potentially exciting work—largely funded by the National Institute of Diabetes, Digestive, and Kidney Disorders (NIDDK) and with the essential support of the Interstitial Cystitis Association (ICA)—is in progress with regard to epidemiology, etiology, and clinical treatment, many clinicians and researchers have used this hiatus to take another look at what exactly is being studied and how the syndrome should be approached. This article explores some of the current "hot-button" issues of definition and nomenclature that have formed the basis of many international meetings in the last 5 years.

## Definition

> "When I use a word," Humpty Dumpty said, in rather a scornful tone, "it means just what I choose it to mean—neither more nor less."
> "The question is," said Alice, "whether you can make words mean so many different things."
> "The question is," said Humpty Dumpty, "which is to be master—that's all." [3]

Tage Hald refered to it as "a hole in the air" [4]. It has been 20 years since the NIDDK proposed diagnostic criteria for entrance into research studies of interstitial cystitis (IC) [5,6], and so inadvertently defined the disorder for a generation of urologists. There has been a change in the way the disease (symptom complex, syndrome?) is perceived, and it is valuable to review briefly some of the ways it has been defined in the past (Box 1).

When the NIDDK-revised criteria were compared with the database entry criteria, it was apparent that up to 60% of patients clinically believed to have IC by experienced clinicians were being missed when the NIDDK research criteria were used as a definition of the disease (Fig. 1) [12].

The lack of clarity in terms of definition is highlighted when looking at the results of numerous epidemiology prevalence studies that show widely disparate results, depending on how the disorder is defined (Fig. 2) [13–18]. These studies show prevalence rates in 100,000 females, from 1.8 when physician-assigned diagnoses were used in Olmstead County, Minnesota, [19] to 450 when patients self-reported a diagnosis in the National Household Interview Survey [20]. Interestingly, rates are surprisingly similar in Finland, Taiwan, and Austria (at about 300) when a high O'Leary-Sant symptom score is used as a surrogate for a diagnosis of IC (see Fig. 2) [21–24].

Unfortunately, histopathology does not help when it comes to defining this symptom. One can have bladder biopsies consistent with the diagnosis of IC, but there is no microscopic picture pathognomonic of this disorder. The role of histopathology in the diagnosis of IC is primarily one of excluding other possible diagnoses. Rosamilia and colleagues reviewed the pathology literature pertaining to IC and presented their own data [25,26]. They compared forceps biopsies from 35 control and 34 IC patients, 6 with bladder capacities less than 400cc under anesthesia. Epithelial denudation, submucosal edema, congestion

*E-mail address:* hannop@uphs.upenn.edu

0094-0143/08/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.ucl.2007.09.011

**Box 1. Historical definitions of interstitial cystitis**

1887 Skene [7]: An inflammation that has destroyed the mucous membrane partly or wholly and extended to the muscular parietes.
1915 Hunner [8]: A peculiar form of bladder ulceration whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment in patients with frequency and bladder symptoms (spasms).
1951 Bourque [9]: Patients who suffer chronically from their bladder; and we mean the ones who are distressed, not only periodically but constantly, having to urinate at all moments of the day and of the night suffering pains every time they void.
1978 Messing and Stamey [10]: Nonspecific and highly subjective symptoms of around-the-clock frequency, urgency, and pain somewhat relieved by voiding when associated with glomerulations upon bladder distention under anesthesia.
1990 Revised NIDDK Criteria: Pain associated with the bladder or urinary urgency, and, glomerulations or Hunner's ulcer on cystoscopy under anesthesia in patients with 9 months or more of symptoms, at least 8 voids per day, 1 void per night, and cystometric bladder capacity less than 350cc [6].
1997 NIDDK Interstitial Cystitis Database Entry Criteria: Unexplained urgency **or** frequency (7 or more voids per day), **OR** pelvic pain of at least 6 months duration in the absence of other definable etiologies [11].

and ectasia, and inflammatory infiltrate were increased in the IC group. Submucosal hemorrhage did not differentiate the groups, but denuded epithelium was unique to the IC group and more common in those with severe disease. The most remarkable finding in this study was that histologic parameters were normal and indistinguishable from control subjects in 55% of IC patients. Method of biopsy can be important in interpreting

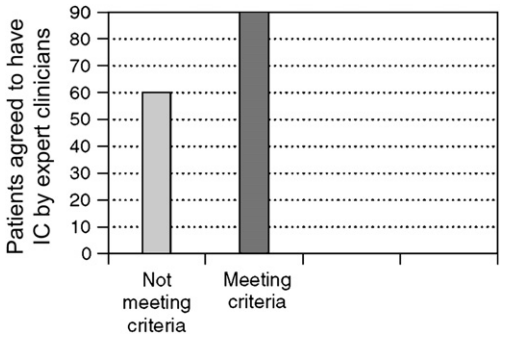


Fig. 1. NIDDK criteria compared with IC database entry criteria; 424 patients with urgency or pain or frequency greater than 6 months (see text for explanation). (*Data from* Hanno PM, Landis JR, Matthews-Cook Y, et al. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol 1999;161(2):553–7.)

findings, because transurethral resection biopsies tend to show mucosal ruptures, submucosal hemorrhage, and mild inflammation [27], whereas histology is normal approximately half the time with cold-cup forceps biopsies [28,29].

Keay's finding [30] that cells from the bladder lining of normal controls grow significantly more rapidly in culture than cells from IC patients, and her subsequent discovery and description of a frizzled 8 protein produced by bladder uroepithelial cells (APF) of IC patients, holds promise as a marker of the disease and, perhaps, a way to define it. As of 2007, neither have her findings been replicated by other centers, nor has a commercially available assay for APF been approved. The use of APF as a diagnostic marker and a part of the clinical definition of the syndrome remains tantalizing but not clinically accessible.

Is there a clinical test that, by virtue of its sensitivity and specificity, could be used to diagnose IC and thereby become a part of the definition of the disorder? Unfortunately, there is not. The potassium chloride test proposed by Parsons and colleagues [31]—an intravesical challenge comparing the sensory nerve provocative ability of saline versus potassium chloride using a 0.4M-KCl solution—has not gained acceptance as a diagnostic test for a variety of reasons [32]. It has neither the specificity nor the sensitivity to be used as a diagnostic test, and therefore results of the test could not be a part of any clinically useful definition.

As the new century dawned, there was much confusion as to how to define this 100-year-old

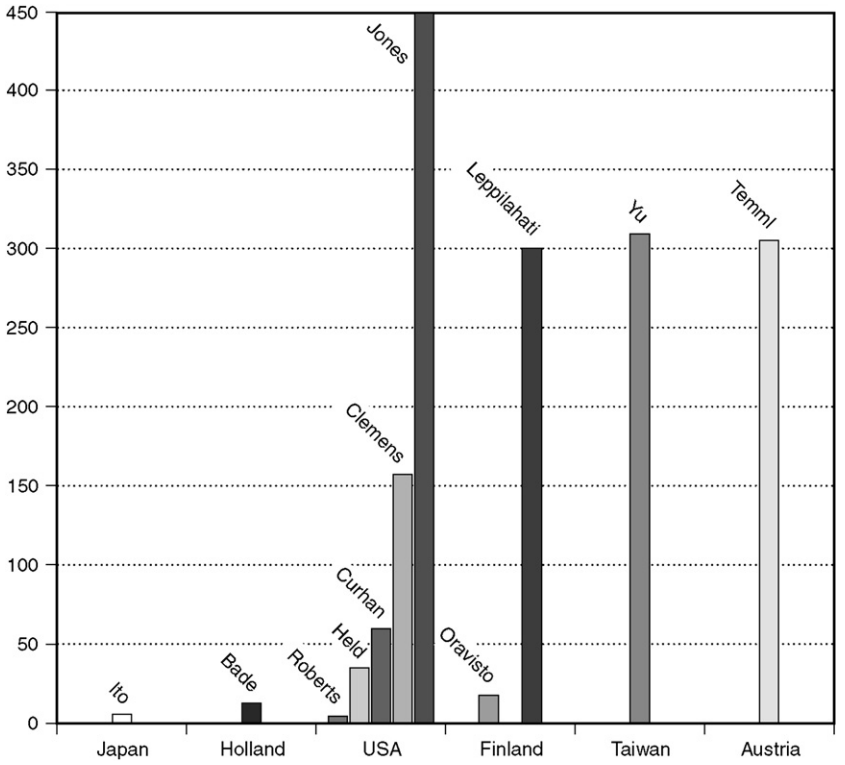


Fig. 2. IC prevalence per 100,000 female population (see text for explanation).

syndrome, and the need for a clinically useful, universally accepted way to characterize IC took to the forefront. Abrams and the International Continence Society (ICS) preferred Bourke's term ''painful bladder'' and defined painful bladder syndrome as ''the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology.'' Rather than drop the designation of IC all together, they limited it to patients with painful bladder who had ''typical cystoscopic and histological features'' without identifying those features [33]. The term ''urgency'' was effectively taken out of the IC equation, and used to identify ''*the complaint of a sudden compelling desire to pass urine which is difficult to defer*.'' It became an integral part of the definition of overactive bladder: *urgency with or without urge incontinence, usually with frequency and nocturia*. Some degree of confusion has resulted [34], and patient organizations have not been happy to give up the urgency term, one that many patients identify with their IC symptoms [35]. When looking at the Interstitial Cystitis Symptom Index (O'Leary-Sant ICSI), the ICSI question for urgency, ''the strong need to urinate with little or no warning,'' consistently yields lower scores than the severity question of ''the compelling urge to urinate that is difficult to postpone'' [36].

Warren [37] compared the ICS painful bladder criteria with symptoms of patients he recruited for a case control study of newly diagnosed women with IC. His criteria for entrance into the study included women greater than 18 years of age with symptom onset within 12 months. They had greater than 4 weeks of perceived bladder pain at or greater than 3 on a 10-point Likert scale and at least two of frequency ($\geq$8/24 hours), urgency ($\geq$3 on a Likert scale), or nocturia. Exclusionary criteria were those of the NIDDK. He found that the ICS definition identified only 66% of his 138 cases. Those who met the definition did not differ from those who did not. The restriction to ''suprapubic pain'' in the ICS definition and the relationship of pain to filling were the criteria most responsible for the poor sensitivity.

Soon after the ICS terminology publication, several high-profile international meetings were held to tackle the problem of definition and nomenclature and establish a new framework for future collaborative research. Although each meeting had long, complex agendas, it is useful to look at how each approached the definition of the syndrome.

The first of these meetings was the International Consultation on Interstitial Cystitis Japan (ICICJ), held in Kyoto in March 2003, under the direction of Ueda, Sant, Yoshimura, and the present author [38]. This meeting concluded by suggesting the following:

> Interstitial cystitis should be suspected and further investigation is recommended in any patients with pelvic pain and urgency and/or urinary frequency associated with no obvious treatable condition/pathology. The term IC should be expanded to a term IC/CPPS (interstitial cystitis/chronic pelvic pain syndrome) when pelvic pain is at least of 3 months duration and associated with no obvious treatable condition/pathology.

The ICICJ was quickly followed by a meeting of a newly formed European Society for the Study of IC (ESSIC). The first meeting was held in Denmark in May 2003, with annual meetings thereafter. A process was begun that culminated in 2005 with the acceptance by ESSIC of the ICS definition of PBS with only minor modification [39]. IC was a subset of PBS defined as:

> A disease of unknown origin consisting of the complaint of suprapubic pain related to bladder filling accompanied by other symptoms, such as increased daytime ($>8\times$) and nighttime ($>1\times$) frequency, and with cystoscopic (glomerulations and/or Hunner's lesions) and/or histological features (mononuclear inflammatory cells including mast cell infiltration and granulation tissue) in the absence of infection or other pathology.

On October 29 2003, the NIDDK convened a meeting of the members of the Interstitial Cystitis Epidemiology Task Force, the IC executive committee, ad hoc participants, and National Institutes of Health staff to review the status of current investigations of IC and to plan new epidemiology investigations [40]. The following served as their working definition:

> Interstitial cystitis is a symptomatic diagnosis based on the presence of three key symptoms: pain, urgency, and frequency, as well as exclusion of a short list of other conditions that cause the same symptoms. Pain is the most consistent and disabling symptom for IC patients. Some will not use the term pain, but will rather describe a sense of pressure or discomfort. Typically, but not always, the pain is worse with filling of the bladder and is relieved by emptying of the bladder. Urgency in IC patients differs from that experienced by patients with urinary incontinence. In IC patients, the urgency is driven by pain, in patients with incontinence (detrusor overactivity), it is driven by their fear of losing control. Not enough information is available on normal variability of urinary frequency to establish a number that can help diagnose IC.

Immediately following the epidemiology meeting, the NIDDK, in conjunction with the ICA, held a basic and clinical science symposium [41]. It concluded: "The struggle to define IC will continue. Bladder pain will continue to be the key to the definition in the near future."

In June 2004 the third International Consultation on Incontinence, cosponsored by the International Consultation on Urological Diseases in official relationship with the World Health Organization, the International Society of Urology, the ICS, and the major international associations of Urology and Gynecology, adopted the ICS definition of IC and PBS. It noted that because of the ambiguity in defining IC as a subset of PBS, the terms would be used together to refer to the same constellation of symptoms (PBS/IC) [25]. Further, it concluded that: "Interstitial cystitis is a clinical diagnosis primarily based on symptoms of urgency/frequency and pain in the bladder and or pelvis. The combined term PBS/IC will be used until more specific criteria can be established."

Soon after the International Consultation on Incontinence, the Multinational Interstitial Cystitis Association met to carry the discussion forward [41]. The group kept the ICS definition of PBS, but broadened the symptom of pain to include "pressure" and "discomfort." The group went on to note:

> Interstitial cystitis may be a subgroup of this larger syndrome (PBS) … but as this remains somewhat vague, a general nomenclature is preferred and the question of what is "IC" alone is left to be determined. Urgency is a common complaint of this group of patients. The ICS definition of urgency could be interpreted as compatible with either detrusor overactivity of PBS/IC. Because the term of urgency would tend to obfuscate the borders of these two conditions and may be unnecessary as a part of the definition of PBS/IC, its place in the definition

will need to be worked out in conjunction with the ICS terminology committee.

The ESSIC presented a comprehensive report at the NIDDK 2006 ''Frontiers in Painful Bladder Syndrome and Interstitial Cystitis'' meeting in October 2006. In response to a decision made public there by the ESSIC to drop the moniker ''interstitial cystitis'' in favor of ''bladder pain syndrome''—which was to be further categorized by results of optional investigations (see below)—the ICA, in conjunction with the Association of Reproductive Health Professionals, held a meeting in Washington, DC. The meeting included a cross-section of invited American urologists, gynecologists, nurses, and representatives from the German patient organization and a urologist from Germany. The following definition was promulgated at the meeting and is available at http://www.arhp.org/healthcareproviders/visitingfacultyprograms/icpbs/whitepaper.cfm: IC/PBS is defined by pelvic pain, pressure, or discomfort related to the bladder, typically associated with persistent urge to void or urinary frequency, in the absence of infection or other pathology.

The term ''persistent urge'' was meant to include the idea of urgency in the definition while not directly impinging on the ICS's use of the term as defined for overactive bladder.

In a compromise presented at the second International Consultation on Interstitial Cystitis Japan, in March 2007, the ESSIC agreed to modify the name and definition to be acceptable to all stakeholders. This was confirmed at their meeting in Muenster, in May 2007.

> Bladder pain syndrome/interstitial cystitis would be diagnosed on the basis of chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptoms like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.
>
> Further documentation and classification of BPB/IC might be performed according to findings at cystoscopy with hydrodistention and morphological findings in bladder biopsies.

## Nomenclature

Following closely on the heals of definition is nomenclature. In many ways this has morphed in to a hot-button issue, and in mid-2007 there is no agreement as to how this complex syndrome should be referred to.

Changes in nomenclature have punctuated the literature over the last 170 years. The syndrome has variously been referred to as tic doloureux of the bladder, IC, cystitis parenchymatosa, Hunner's ulcer, panmural ulcerative cystitis, urethral syndrome, and PBS [7,9,42–46]. The term ''interstitial cystitis,'' which Skene is credited with coining and Hunner for bringing it in to common usage, is somewhat of a misnomer; in many cases not only is there no interstitial inflammation, but also, histopathologically, there may be no inflammation at all [26,28,47,48].

With the formal definition of the term ''painful bladder syndrome'' by the ICS in 2002 [33], the terminology discussion began to take on an importance and priority not seen for decades. Perhaps the lack of progress in identifying causes of the disorder and effective treatments might somehow be related to an improper focus solely on bladder pathology, partly as a result of the potentially misleading name of the disorder. Was the perspective of researchers and clinicians somehow off target, and should this disorder be looked at as part of a new paradigm (perhaps through a pain paradigm)?

In Kyoto at the ICICJ in March 2003, it was agreed that the term ''interstitial cystitis'' should be expanded to ''interstitial cystitis/chronic pelvic pain syndrome'' when pelvic pain is at least of 3 months duration and associated with no obvious treatable condition/pathology [38]. The ESSIC held its first meeting in Copenhagen soon after Kyoto. Nomenclature was discussed, but no decision was reached, as the meeting concentrated on how to evaluate patients for diagnosis [49]. At the 2003 meeting of the NIDDK titled, ''Research Insights into Interstitial Cystitis,'' it was concluded that ''interstitial cystitis'' will inexorably be replaced as a *sole* name for this syndrome. It will be a gradual process over several years. At the meeting it was referred to as ''interstitial cystitis/painful bladder syndrome'' in keeping with ICS nomenclature [41].

At the 2004 meeting of the Multinational Interstitial Cystitis Association in Rome, it was concluded that the syndrome should be referred to as ''painful bladder syndrome/interstitial cystitis'' or ''PBS/IC'' [41]. That same year, the International Consultation on Incontinence, cosponsored by the ICS and Societe Internationale d''Urologie in association with the World Health Organization, included the syndrome as a part of the consultation. Interestingly, the chapter in the report was titled, ''painful bladder syndrome (including

interstitial cystitis),'' suggesting that the IC formed an identifiable subset within the broader syndrome. Because such a distinction is difficult to define, within the body of the chapter, co-authored by nine committee members and five consultants from four continents, it was referred to as PBS/IC (one inclusive entity) [25].

In June 2006 Abrams and colleagues [50] published an editorial that attacked the nomenclature problem head-on. They noted that:

> It is an advantage if the medical term has clear diagnostic features that translate to a known pathophysiologic process so that effective treatment may be given. Unfortunately, the latter is not the case for many of the pain syndromes suffered by patients seen at most pain, gynecological, and urological clinics. For the most part these ''diagnoses'' describe syndromes that do not have recognized standard definitions, yet infer knowledge of a pathophysiologic cause for the symptoms. Unfortunately the terminology used to describe the condition may promote erroneous thinking about treatment on the part of physicians, surgeons and patients. These organ based diagnoses are mysterious, misleading and unhelpful, and can lead to therapies that are misguided or even dangerous.

The editorial went on to note that a single pathologic descriptive term (interstitial cystitis) for a spectrum of symptom combinations ill serves patients. The umbrella term ''painful bladder syndrome'' was proposed, with a goal to define and investigate subsets of patients who could be clearly identified within the spectrum of PBS. It would fall within the rubric of chronic pelvic pain syndrome. Sufferers would be identified according to the primary organ that *appears* to be affected on clinical grounds. Pain not associated with an individual organ would be described in terms of the symptoms. One can see in this the beginnings of a new paradigm that might be expected to change the emphasis of both clinical and basic science research, and that removes the automatic presumption that the end-organ in the name of the disease should necessarily be the sole or primary target of such research.

At the major biannual IC research conference in the fall of 2006, held by the NIDDK (Frontiers in Painful Bladder Syndrome—PBS and Interstitial Cystitis), the ESSIC group was given a block of time with which to present their thoughts and conclusions [51]. Because PBS did not fit into the taxonomy of other pelvic pain syndromes such as urethral or vulvar pain syndromes, and because IC is open to different interpretations, ESSIC decided to rename PBS as bladder pain syndrome (BPS), followed by a type designation. BPS is indicated by two symbols, the first of which corresponds to cystoscopy with hydrodistention findings (1, 2, or 3, indicating increasing grade of severity) and the second to biopsy (A, B, and C, indicating increasing grade of severity of biopsy findings). Although neither cystoscopy with hydrodistention nor bladder biopsy was prescribed as an essential part of the evaluation, by categorizing patients as to whether either procedure was done, and if so, the results, it is possible to follow patients with similar findings and study each identified cohort to compare natural history, prognosis, and response to therapy.

Table 1 shows the layout of this type of classification with notation as to what previously was termed ''PBS'' and what would fall into past definitions of IC. Both terms become superfluous for purposes of categorization if one adopts the ESSIC classification of BPS with the appropriate letter and number. As Baranowski [52] conceives it, BPS is thus defined as pain with a collection of symptoms, the most important of which is pain perceived to be in the bladder. IC is distinguished as an end-organ, visceral-neural pain syndrome, whereas BPS can be considered a pain syndrome that involves the end-organ (bladder) and neuro-visceral (myopathic) mechanisms. In IC, one expects end-organ primary pathology. This is not necessarily the case in the broader BPS (Table 1).

Another way to conceptualize this is with the drawing of a target (Fig. 3).

There may be many causes of chronic pelvic pain. When an etiology cannot be determined, it is characterized as pelvic pain syndrome. To the extent that it can be distinguished as urologic, gynecologic, dermatologic, and the like, it is further categorized by organ system. A urologic pain syndrome can sometimes be further differentiated on the site of perceived pain. Bladder, prostate, testicular, and epididymal pain syndromes follow. Finally, types of BPS can be further defined as IC, or simply categorized by ESSIC criteria. This new perspective, which remains in its formative stages, will likely be presented in a more crystallized form by Andrew Baranowski as a part of the International Association for the Study of Pain Conference, in Glasgow in 2008.

Patient groups have expressed significant reservations with regard to any nomenclature change

Table 1
Classification of bladder pain syndrome by the European Society for the study of Interstitial Cystitis (see text for explanation)

**ESSIC Classification of BPS**

| BIOPSY \ CYSTOSCOPY WITH HYDRODISTENTION | Not Done | Normal | Glomerulations | Hunner Lesion |
|---|---|---|---|---|
| Not Done | XX PBS | 1X PBS | 2X IC | 3X IC |
| Normal | XA PBS | 1A PBS | 2A IC | 3A IC |
| Inconclusive | XB PBS | 1B PBS | 2B IC | 3B IC |
| Positive | XC IC | 1C IC | 2C IC | 3C IC |

Nordling J and van de Merwe JP. ESSIC web site, Accessed, September 2006.

(*Data from* Nordling J. ESSIC classification of BPS/IC. European Opinion on PBS/IC Characterizations. Presented at the 2006 International Symposium Frontiers in Painful Bladder Syndrome and Interstitial Cystitis, National Institute of Diabetes and Digestive and Kidney Disease. Bethesda, MD, October 26–27, 2006.)

that potentially drops the "interstitial cystitis" moniker. The meeting organized by the Association of Reproductive Health Professionals and the ICA concluded that:

> The nomenclature of IC/PBS may need to change, but change should not be undertaken now because there is insufficient evidence to support a change. Any change in nomenclature should be evidence-based. This group favors retaining IC in whatever name is considered in the future and positioning it first, as in IC/PBS [35].

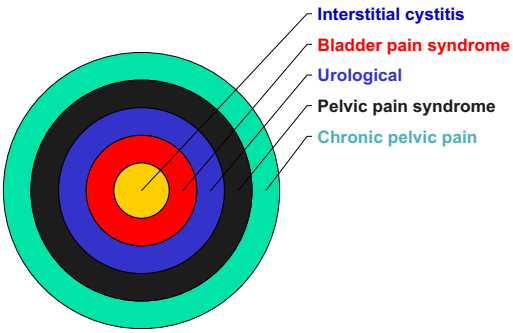


Fig. 3. Proposed classification system for chronic pain syndromes, where IC might fit in (initial proposal by Baronowski [51]). (*Data from* Nordling J. ESSIC classification of BPS/IC. European Opinion on PBS/IC Characterizations. Presented at the 2006 International Symposium Frontiers in Painful Bladder Syndrome and Interstitial Cystitis, National Institute of Diabetes and Digestive and Kidney Disease. Bethesda, MD, October 26–27, 2006.)

Their objections include the following:

1. BPS is too broad a term
2. Name change will result in decreased recognition of the syndrome after years of efforts to increase awareness of the name IC
3. Patients, legislators, and the general public will be adversely impacted by a name change
4. The U.S. Social Security Administration and private insurance recognizes IC but not the term BPS, and benefits could be adversely affected
5. A negative impact on research funding is possible
6. A negative impact on literature searches and information gathering is possible

As a result of these concerns, the ESSIC plans to append the IC term to the BPS nomenclature for the foreseeable future, referring to the syndrome as BPS/IC.

## Next steps

The worldwide community of health care professionals rely on the use of a single medical

language to communicate. Ideally, terminology should be easily recognizable throughout the global medical community. Although much of the discussion may seem pedantic, it is in reality of the utmost importance and represents nothing short of a new paradigm with which to view the IC syndrome in a new context. Efforts to establish a consensus for a clinical definition, nomenclature, and diagnostic algorithm through the auspices of the American Urological Association and the European Association of Urology are underway. The NIDDK is planning similar meetings to bring together a definition and appropriate nomenclature for the clinical and basic research community. It is hoped that these efforts will be somehow linked to provide a conclusion satisfactory to all stakeholders, and which is consistent worldwide. Hopefully, the U.S. Food and Drug Administration will find the efforts worthwhile, and signal the pharmaceutical industry how best to proceed with clinical research studies based on the paradigm so that the field can advance for the benefit of all patients.

## References


[1] Keay S, Warren JW. A hypothesis for the etiology of interstitial cystitis based upon inhibition of bladder epithelial repair. Med Hypotheses 1998;51(1): 79–83.

[2] Keay SK, Szekely Z, Conrads TP, et al. An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. Proc Natl Acad Sci USA 2004;101(32):11803–8.

[3] Carroll L. Humpty dumpty. Through the looking glass. Public Domain; 1871.

[4] George NJR. Preface. In: George NJR, Gosling JA, editors. Sensory disorders of the bladder and urethra. Berlin: Springer-Verlag; 1986. p. vii.

[5] Gillenwater JY, Wein AJ. Summary of the national institute of arthritis, diabetes, digestive and kidney diseases workshop on interstitial cystitis, National Institutes of Health, Bethesda, Maryland, August 28–29, 1987. J Urol 1988;140(1):203–6.

[6] Wein A, Hanno PM, Gillenwater JY. Interstitial cystitis: an introduction to the problem. In: Hanno PM, Staskin DR, Krane RJ, et al, editors. Interstitial cystitis. London: Springer-Verlag; 1990. p. 3–15.

[7] Skene AJC. Diseases of the bladder and urethra in women. New York: William Wood; 1887.

[8] Hunner GL. A rare type of bladder ulcer in women; report of cases. Boston Med Surg Journal 1915;172: 660–4.

[9] Bourque JP. Surgical management of the painful bladder. J Urol 1951;65:25–34.

[10] Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. Urology 1978;12(4):381–92.

[11] Simon LJ, Landis JR, Tomaszewski JE, et al. The interstitial cystitis database (ICDB) study. In: Sant GR, editor. Interstitial cystitis. Philadelphia: Lippincott-Raven; 1997. p. 17–24.

[12] Hanno PM, Landis JR, Matthews-Cook Y, et al. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol 1999;161(2): 553–7.

[13] Oravisto KJ. Epidemiology of interstitial cystitis. Ann Chir Gynaecol Fenn 1975;64(2):75–7.

[14] Ito T, Miki M, Yamada T. Interstitial cystitis in Japan. BJU Int 2000;86(6):634–7.

[15] Held PJ, Hanno PM, Wein AJ. Epidemiology of interstitial cystitis: 2. In: Hanno PM, Staskin DR, Krane RJ, et al, editors. Interstitial cystitis. London: Springer-Verlag; 1990. p. 29–48.

[16] Curhan GC, Speizer FE, Hunter DJ, et al. Epidemiology of interstitial cystitis: a population based study. J Urol 1999;161(2):549–52.

[17] Clemens J, Meenan R, Rosetti M, et al. Prevalence and incidence of interstitial cystitis in a managed care population. J Urol 2005;173:98–102.

[18] Bade JJ, Rijcken B, Mensink HJ. Interstitial cystitis in The Netherlands: prevalence, diagnostic criteria and therapeutic preferences. J Urol 1995;154(6): 2035–7.

[19] Roberts RO, Bergstralh EJ, Bass SE, et al. Incidence of physician-diagnosed interstitial cystitis in Olmsted County: a community-based study. BJU Int 2003;91(3):181–5.

[20] Jones CA, Nyberg L. Prevalence of interstitial cystitis in the United States [Abstract]. J Urol 1994;151: 423A.

[21] Yu H-J. Prevalence of interstitial cystitis in Taiwan. Presented at Pan Asian Interstitial Cystitis Conference, Tapei, Taiwan, April 2006.

[22] Temml C, Wehrberger C, Riedl C, et al. Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. Eur Urol 2007;51(3):803–8.

[23] Leppilahti M, Tammela TL, Huhtala H, et al. Prevalence of symptoms related to interstitial cystitis in women: a population based study in Finland. J Urol 2002;168(1):139–43.

[24] Leppilahti M, Sairanen J, Tammela TL, et al. Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finland. J Urol 2005;174(2):581–3.

[25] Hanno P, Baranowski A, Fall M, et al. Painful bladder syndrome (including interstitial cystitis). In: Abrams PH, Wein AJ, Cardozo L, editors. Incontinence. 3rd edition. Paris: Health Publications Limited; 2005. p. 1456–520.

[26] Rosamilia A, Igawa Y, Higashi S. Pathology of interstitial cystitis. Int J Urol 2003;10 Suppl:S11–5.

[27] Johansson SL, Fall M. Clinical features and spectrum of light microscopic changes in interstitial cystitis. J Urol 1990;143(6):1118–24.
[28] Lynes WL, Flynn SD, Shortliffe LD, et al. The histology of interstitial cystitis. Am J Surg Pathol 1990;14(10):969–76.
[29] Mattila J. Vascular immunopathology in interstitial cystitis. Clin Immunol Immunopathol 1982;23(3): 648–55.
[30] Keay S, Zhang CO, Marvel R, et al. Antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor: sensitive and specific urine markers for interstitial cystitis. Urology 2001;57(6 Suppl 1):104–7.
[31] Parsons CL, Greenberger M, Gabal L, et al. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. J Urol 1998;159(6): 1862–6.
[32] Hanno P. Is the potassium sensitivity test a valid and useful test for the diagnosis of interstitial cystitis? Int Urogynecol J Pelvic Floor Dysfunct 2005;16(6): 428–9.
[33] Abrams PH, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society. Neurourology and Urodynamics 2002;21:167–78.
[34] Abrams P, Hanno P, Wein A. Overactive bladder and painful bladder syndrome: there need not be confusion. Neurourol Urodyn 2005;24(2):149–50.
[35] Outcome of the Washington, DC, Consensus Meeting on Interstitial Cystitis/Painful Bladder Syndrome: Association of Reproductive Health Professionals; 2007.
[36] Diggs C, Meyer WA, Langenberg P, et al. Assessing urgency in interstitial cystitis/painful bladder syndrome. Urology 2007;69(2):210–4.
[37] Warren JW, Meyer WA, Greenberg P, et al. Using the International Continence Society's definition of painful bladder syndrome. Urology 2006;67(6): 1138–42.
[38] Ueda T, Sant G, Hanno P, et al. International Consultation on Interstitial Cystitis Japan. International Journal of Urology 2003;10(Supplement):1–70.
[39] Van De Merwe J, Nordling J. Interstitial cystitis: definitions and confusable diseases; ESSIC meeting 2005 Baden. European Urology Today [March 2006], 14–17, 2006.
[40] Vaughn ED, Wilt T, Hanno P, et al. Epidemiology of interstitial cystitis, executive committee summary and task force report. 2004 Oct 29; Two Democracy Plaza, 7'th Floor. Bethesda (MD): National Institutes of Health; 2003.
[41] Hanno P, Keay S, Moldwin R, et al. International Consultation on IC—Rome, September 2004. Forging an International Consensus: progress in painful bladder syndrome/interstitial cystitis. Report and abstracts. Int Urogynecol J Pelvic Floor Dysfunct 2005;16(Suppl 1):S2–34.
[42] Christmas TJ. Historical aspects of interstitial cystitis. In: Sant GR, editor. Interstitial cystitis. Philadelphia: Lippincott-Raven; 1997. p. 1–8.
[43] Hunner GL. A rare type of bladder ulcer. Further notes, with a report of eighteen cases. JAMA 1918; 70(4):203–12.
[44] Parsons JK, Parsons CL. The historical origins of interstitial cystitis. J Urol 2004;171(1):20–2.
[45] Powell NB, Powell EB. The female urethra: a clinicopathological study. J Urol 1949;61:557–70.
[46] Teichman JM, Thompson IM, Taichman NS. Joseph Parrish, tic doloureux of the bladder and interstitial cystitis. J Urol 2000;164(5):1473–5.
[47] Denson MA, Griebling TL, Cohen MB, et al. Comparison of cystoscopic and histological findings in patients with suspected interstitial cystitis. J Urol 2000;164(6):1908–11.
[48] Tomaszewski JE, Landis JR, Russack V, et al. Biopsy features are associated with primary symptoms in interstitial cystitis: results from the interstitial cystitis database study. Urology 2001;57(6 Suppl 1):67–81.
[49] Nordling J. Overview of the European Copenhagen workshop on interstitial cystitis, Denmark—May 2003. Int Urogynecol 2005;16(S):14–5.
[50] Abrams P, Baranowski A, Berger R, et al. A new classification is needed for pelvic pain syndromes—are existing terminologies of spurious diagnostic authority bad for patients? J Urol 2006;175:1989–90.
[51] NIDDK. Frontiers in Painful Bladder Syndrome and Interstitial Cystitis, 2006. Available at: http://www3.niddk.nih.gov/fund/other/niddkfrontiers/. Accessed October 13, 2007.
[52] Baranowski AP, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an essic proposal. European Urology 2007. doi:10.1016/j.eururo.2007.10.010.